

# THE ROCKEFELLER UNIVERSITY

*pro bono humani generis*

1230 YORK AVENUE - NEW YORK, NEW YORK 10021-6399

*Joshua Lederberg*  
UNIVERSITY PROFESSOR

November 8, 1996

Dr. Stephen C. Joseph  
Assistant Secretary of Defense  
(Health Affairs)  
Defense Pentagon  
Washington, D.C. 20301-1200

Dear Dr. Joseph:

I am glad to have an opportunity to respond to your query of 25 October about the prospects of genetic manipulation of *B. anthracis* aimed at evading the protective-antigen (PA) vaccine now available and under consideration for routine administration to our troops.

Genetic manipulation in this context is not a simple or straight-forward matter. I doubt that it could be achieved in merely a few years. There are many uncertainties, and success of such an enterprise could not be guaranteed. The PA factor in *B. anthracis* plays a key role in the transport of toxins into the target cell. What is unpredictable is whether this biological activity could be preserved in a mutant (genetically engineered) protein that had been so altered as to evade neutralization by PA-antibody. This has not yet been observed in the natural evolution of anthrax. For the most cogent, first-hand expertise I would refer you to R.J. Collier at Harvard University.

I note further that it would be particularly costly to validate the effectiveness (in a military context) of a novel infectious agent, in contrast to the accumulated experience with anthrax. Finally, one side effect of developing a new etiological agent is the concomitant of an easily identifiable signature, making it harder to avoid attribution.

All these points should not diminish concern about genetic reengineering in the longer term. If I had to guess, I would concur that a determined adversary, willing to make investments in the multi-hundred million dollar range, would have a reasonable chance of success over a period of a decade. Countries like Russia, China, and India have the technical and intellectual resources to undertake such a project. We would want to make intelligence efforts to identify any such attempts.

One has to be cautious about underestimating other nations or non-state groups. I believe, however, that this level of breakthrough would be astonishing for the rogue states, and even more improbable for terrorist organizations. As these present a major source of threat and, in the case of terrorist groups, are not easily deterred, I would highly value anthrax inoculation in this context.

If genetic reengineering would take a decade or more, I would hope that we would use this time to make comparable investments in the development of new approaches to defending our personnel against these and a range of other biological threats. For *B. anthracis* in particular, experimental vaccines that directly neutralize other of its toxins have already been demonstrated, but need further testing to reach the standards of FDA registration. Other approaches are being actively cultivated by DARPA. It is the protection of the current force over the next few years that is the issue.

Finally, to counter an anthrax vaccination program, a far easier path would be for an adversary to adopt other familiar pathogens -- plague and tularemia are examples. Our gains from forcing such a shift would, however, be real. Other bacterial agents have shortcomings compared to the aerosol-tolerant spore-forming anthrax. Moreover, these other diseases are generally easier to treat ex-post facto. Still, it follows from this that vaccination against anthrax must be part of a multi-pronged strategy responding to a range of threat agents, in the realms both of post-exposure management and of prophylaxis. In that context, I strongly support the initiative.

Yours sincerely,

  
Joshua Lederberg